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Small cell lung cancer: Results of a phase II study of 1,2,4 triglycidylurazol

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Summary. Fourteen patients with small cell lung cancer (SCLC) received treatment with 1,2,4 triglycidylurazol (TGU) 600 mg/m^2 or 800 mg/m^2 as an IV bolus every 4 weeks. Twelve patients had received previous chemotherapy consisting of a five-drug regimen given for the short duration of only 9 weeks. All had measurable disease. Following TGU 11 patients had progressive disease and 3 patients had stable disease. The most frequent toxicity was nausea and vomiting, which occurred in all patients but was generally mild. Myelosuppression was common with a median white blood count nadir of 2.5×10^9/l (range $0.9-7.4 \times 10^9$/l) and median platelet count nadir of 76×10^9/l (range $5-173 \times 10^9$/l). Alopecia, thrombophlebitis, and hepatic or renal toxicity were not observed.

In this study, TGU had no activity in SCLC, and the dose-limiting toxicity was myelosuppression.

Introduction

Small cell lung cancer (SCLC) is sensitive to a variety of cytotoxic drugs. However, our ability to cure most patients with this disease has been impeded by the high proportion of patients who show an initial response to chemotherapy and then subsequently relapse. Furthermore, practically no patients with extensive disease at presentation will survive 3 years [5]. Dose escalation of existing cytotoxic drugs has failed to overcome these problems [2], and it is obviously important to continue to investigate new drugs to improve the treatment of this cancer.

TGU (1,2,4 triglycidylurazol) is a triepoxide which has been shown to have activity in a number of murine tumours and probably functions as an alkylating agent [1]. In phase I studies, the dose-limiting toxicity of TGU was reported as myelosuppression, and a dose of 650–800 mg/m^2 was recommended for future phase II studies [3, 6]. Moreover, in one of these studies, TGU showed promising antitumour activity [6]. Therefore, in view of the activity of other alkylating agents, such as cyclophosphamide [5], in SCLC, we activated this phase II study to investigate TGU in previously untreated patients who had extensive disease at presentation and patients who had relapsed or were refractory to first-line combination chemotherapy.

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Patients and methods

Patients. To be eligible for study entry patients had to fulfil the following criteria: no radiotherapy or chemotherapy during the last 4 weeks, no prior radiotherapy to areas of measurable disease, white blood count (WBC) $>4.0 \times 10^9$/l, platelets $>100 \times 10^9$/l, serum creatinine <120 μmol/l, serum bilirubin <30 μmol/l, and no previous malignancies at other sites. Between February 1984 and February 1985, 14 patients with a mean age of 55 years (range 35–72) entered the study. All had histologically proven SCLC and all had measurable disease. Performance status (ECOG) was 1 in 12 and 2 in 2 patients; 5 patients had limited disease and 9, extensive disease. Twelve had received previous chemotherapy consisting of cyclophosphamide 750 mg/m^2 on day 1, adriamycin 40 mg/m^2 on day 1, etoposide 100 mg/m^2 on days 1–3, methotrexate 50 mg/m^2 on day 10 and vincristine 2 mg on day 10 (CAVMO) [2], all given IV every 21 days for three cycles. Two patients, both with extensive disease, had not received chemotherapy in the past. Of the 12 patients previously treated with CAVMO, 8 had relapsed following a complete remission (CR) and 4 had a partial remission (PR). Radiotherapy (4000 cGy) had been given to the mediastinum in 5 of the patients in the CR group after CAVMO.

Treatment protocol. TGU was supplied as a sterile, lyophilized powder in vials containing 100 mg TGU and 20 mg *d*-mannitol. Each vial was diluted in 5 ml sterile water before administration as an IV bolus, and after administration of the TGU the IV line was flushed with 20 ml normal saline. For patients who had received previous chemotherapy a starting dose of 600 mg/m^2 was used and for those patients without prior chemotherapy a dose of 800 mg/m^2. Treatment was repeated at 28-day intervals and drug administration was postponed by 1 week if the WBC was <3000 or the platelet count, $<100\,000$. Thereafter, dosage modification was as shown in Table 1. If after 3 weeks' delay there was incomplete haematological recovery treatment was terminated. At least two courses of treatment were given unless the patient had progressive disease or experienced excessive toxicity. All patients were given prophylactic antiemetic therapy consisting of IV metoclopromide 10 mg and were provided with a supply of metoclopromide tablets (10 mg) to be taken as required.

Response to treatment assessed using standard WHO criteria [4]. Patients were reviewed weekly, when WBC,

Table 1. Modification of the dose of TGU according to myelosuppression

White blood cell count	Platelets	Dose (%)
≥4000	≥100000	120
2000–4000	75000–99999	100
1000–1999	50000–74999	75
<1000	<50000	50

platelets and haemoglobin were measured. Clinical examination was performed every 4 weeks in addition to measurement of serum urea, electrolytes, transaminases, alkaline phosphatase and bilirubin and chest radiograph.

Results

The 14 patients received 19 cycles of TGU. Eleven patients had progressive disease and 3 patients had stable disease. There were no treatment-related deaths. The most frequent toxicity was nausea and vomiting, which was experienced by all patients despite prophylactic antiemetic therapy. The emesis was generally mild and was of less than 60 min duration in 12 patients. Only 2 patients had persistent nausea and vomiting of over 12 h duration. Myelosuppression was also frequent. Using WHO grading [4] the WBC nadir was grade 0 in 4 patients, grade II in 5, grade III in 3 and grade IV in 2, and the platelet nadir was grade 0 in 4, grade I in 4, grade II in 3, grade III in 2 and grade IV in 1. The median WBC nadir was 2.5×10^9/l (range $0.9–7.4 \times 10^9$/l), occurring on median day 14 after chemotherapy, with recovery by median day 28. The median platelet nadir was 76×10^9/l (range $5–173 \times 10^9$/l), occurring on median day 14 after chemotherapy with recovery by median day 28. There was no renal or hepatic toxicity observed. No patients developed alopecia, and all patients with alopecia prior to treatment wiht TGU reported regrowth of hair. Thrombophlebitis was not observed.

Discussion

TGU had no significant antitumour activity in this group of patients with SCLC. This apparent lack of activity was possibly due to the high proportion of patients who had previously been treated with the five-drug combination chemotherapy regimen. Indeed, etoposide, which is now regarded as one of the most active agents in SCLC, had extremely variable activity in phase II studies, ranging from 4% to 58% [5]. This usually reflected the number of patients who had been given chemotherapy and presumably had developed drug resistance [5]. Similarly, it is possible that there is complete cross resistance between TGU and the alkylating agents used in our first-line chemotherapy. However, it should be stressed that the duration of treatment with first-line chemotherapy with CAVMO was short – only 9 weeks – and responses to second-line chemotherapy were therefore more likely, especially in those patients who had initially responded then relapsed.

Administration of TGU by the IV bolus technique prevented the development of thrombophlebitis, which had been reported in our phase I study when the drug was given as a short IV infusion [6]. Clearly, reducing the time for which the drug was in contact with endothelium of the smaller veins was important in the abolition of this toxicity. The major toxicity of TGU was myelosuppression. In two patients the myelosuppression was very severe, with profound neutropenia and marked thrombocytopenia. Recovery from myelosuppression generally occurred by day 28 after chemotherapy, but in one patient the myelosuppression was more prolonged, which suggests that TGU may be associated with cumulative myelotoxicity, an observation already commented upon by others [3]. One advantage of TGU was the lack of alopecia. In fact, regrowth of hair occurred in all patients who on study entry were suffering from alopecia related to first-line chemotherapy.

This phase II study of TGU has produced disappointing results. TGU had no activity in patients with SCLC and was associated with significant toxicity, especially myelosuppression, when administered as a dose of 600 mg/m^2.

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